EFFECT OF HYPEROXIA ON DYNAMICS OF ERYTHROPOIESIS IN ANIMALS

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The response of the red blood (the erythron) acquires especial significance when an animal lives in an atmosphere with a modified partial pressure of oxygen.

Most workers who have studied the effect of an oxygen enriched environment on the red blood have observed inhibition of erythropoiesis [5, 8]. However, in some cases a hyperoxic environment may, on the contrary, stimulate erythropoiesis [1, 2, 11].

In our previous investigations [3], when albino mice were kept for short times and for periods of 10 days in an atmosphere with an increased partial pressure of oxygen, the effect was mainly to cause signs of inhibition of regeneration of the red blood.

The present investigation is an attempt to carry the study of the effect of oxygen on erythropoiesis a stage further. Experiments were carried out on animals exposed to more intensive or more prolonged hyperoxia.

To obtain a more accurate picture of the dynamics of regeneration of the red blood of the experimental animals, in addition to the usual methods of analysis in a series of experiments the method of determining the resistance of the erythrocytes to acid hemolysis was used [7]. The acid resistance of the erythrocytes reflects the relative proportions of younger and older cells. The index of resistance was used as criterion. The higher this index, the higher the mean resistance and, consequently, the higher the percentage of young erythrocytes in the blood tested. /299

Experiments were performed on CC55W albino mice and Wistar albino rats aged 2-3 months. Blood was taken from the tail. About 100 animals were used in each series of experiments.

In the experiments of series I the mice were kept continuously for 15 days in an atmosphere consisting of 60% oxygen and 40% nitrogen. Blood was taken several times both during and after exposure.

As Fig. 1 shows, the erythrocyte count fell during the first days of existence in the hyperoxic medium and at the beginning of the recovery period, while on the remaining days it was slightly below the initial level. The hemoglobin concentration likewise was slightly lower, but by the end of exposure and, in particular, after a return to ordinary air, it rose appreciably.

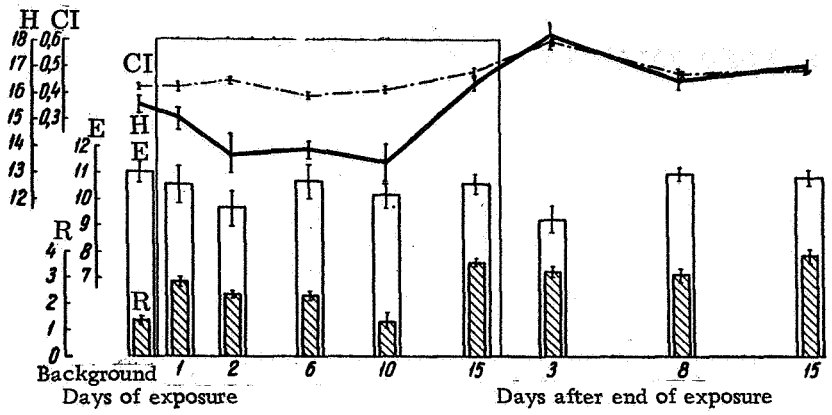

Figure 1. Effect of Exposure for 15 Days to a Medium with 60% O_2 Content on Red Blood of Mice:

CI Color Index; E — Erythrocytes, in Millions/mm^3; R — Reticulocytes, %; H — Hemoglobin.

The reticulocyte count in the blood of the mice exposed to a hyperoxic atmosphere was increased (except on the 10th day), reaching a maximum on the 15th day, and the level remained high after the end of exposure.

Hence, a long exposure to a relatively moderate degree of hyperoxia had a tendency to stimulate erythropoiesis in mice. The small decrease in the erythrocyte count and hemoglobin concentration in the peripheral blood may be attributed to retention of blood in depots under the influence of oxygen excess [6].

In the next series of experiments a short exposure to intensive hyperoxia was /300 given. Albino mice inhaled oxygen at a pressure of 2.5 atm. for 90 min.

The erythrocyte count in the blood of the experimental animals (Fig. 2) after the experiment was only slightly different from before; a small decrease was found on the 6th day only. The percentage of hemoglobin showed no statistically significant deviation in either this or the next two series of experiments, and it is therefore not shown.

Soon after removal of the mice from the chamber, an increase in their reticulocyte count was observed. Since it was too soon for changes in hemopoiesis to become manifest, this increase probably indicates a redistribution of the blood cells under the influence of a hyperoxic environment [2]. Two days after the experiment the percentage of reticulocytes fell below the initial level, but then rose again; at about the 10th day this index had fallen again considerably, returning to normal by the 15th day. It is easy to see that the index of resistance of the erythrocytes shows similar periods of rise and fall, although these fluctuations do not coincide completely in time with changes in the reticulocyte count.

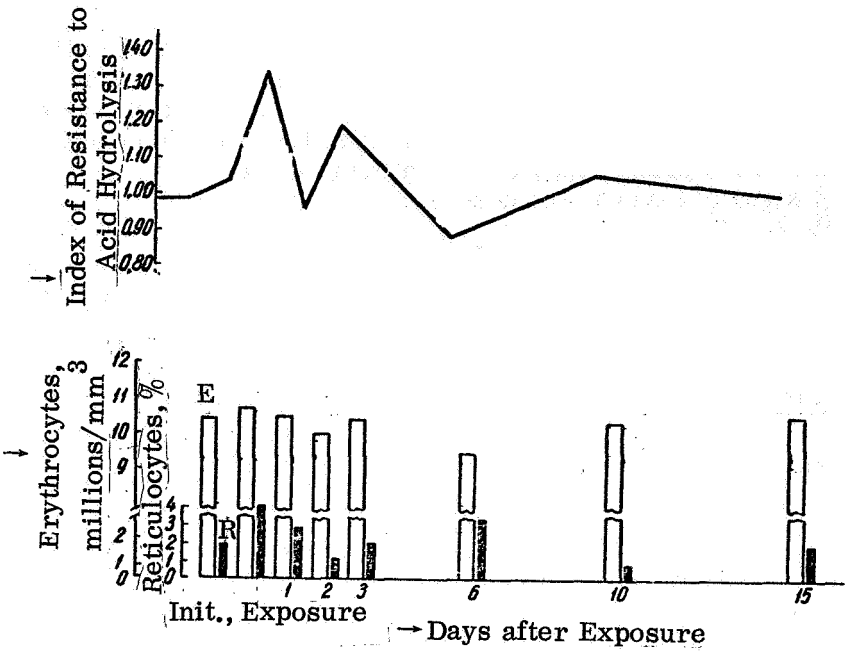

Figure 2. Effect of Exposure for 90 min to O_2 Under Pressure (2.5 abs. atm.) on Red Blood of Mice. Legend as in Fig. 1.

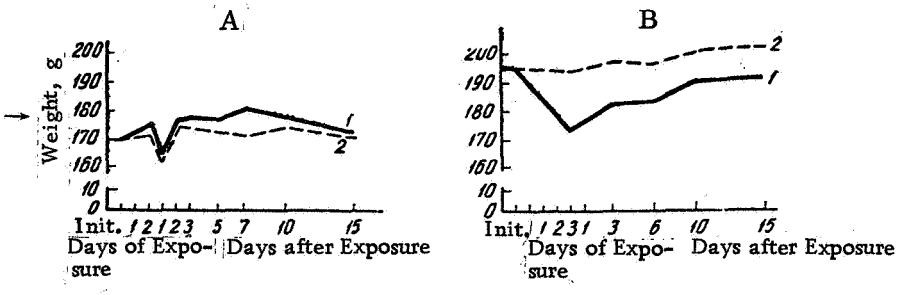

Figure 3. Effect of Exposure to O_2 for 40 h (A) and 72 h (B) on Weight of Rats. 1) Experimental Group; 2) Control.

Exposure to compressed oxygen thus caused a periodic alternation of a rise and fall in the number of young erythrocytes entering the bloodstream. /301

In the experiments of series III rats were placed for 40 h in an atmosphere containing 97% O_2 at normal atmospheric pressure.

Exposure of this duration did not necessarily cause the animals to develop toxic effects from the action of oxygen. Admittedly, the body weight of the rats was lowered for a short time after exposure (Fig. 3, A), but this was due to the stressor action of the experimental situation: similar changes in weight occurred in the rats of a control group exposed to an atmosphere of air in the chamber. The absence of signs of oxygen poisoning is also demonstrated by the curve of respiration rate (Fig. 4, A): in an atmosphere of oxygen the animals' breathing became slower, in agreement with data in the literature [6, 10, 13], returning to the normal rhythm when they were replaced in an atmosphere of air.

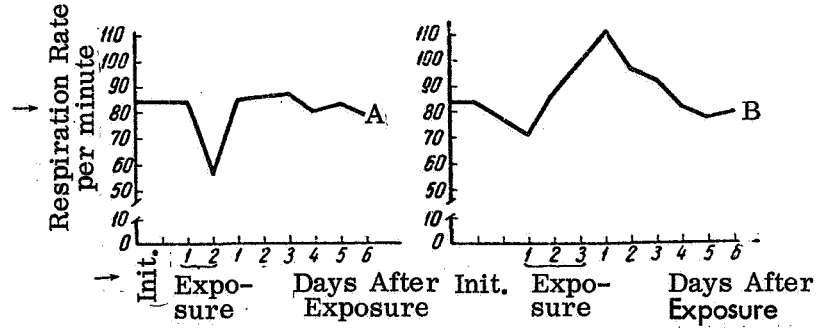

Figure 4. Effect of Exposure to O_2 for 40 h (A) and 72 h (B) on Respiration Rate of Rats.

After the end of the exposure, the number of erythrocytes circulating in the blood of the experimental rats increased (Fig. 5), on account of the redistribution of the blood already mentioned. Later the erythrocyte count fell (reaching a minimum on the 5th day), but by the 15th day it was a little above normal. /302

The reticulocyte count showed a considerable decrease on the 2nd day after the end of exposure, exceeded the initial level on the 10th, and was back to normal on the 15th day. After a short period of decrease, the acid resistance of the erythrocytes rose and remained high throughout the period of observation.

To judge from the index of resistance of the erythrocytes, marked rejuvenation of the red cell composition of the blood was observed. However, this conclusion is contradicted to some extent by the low percentage of reticulocytes which persisted for 5-7 days after the experiment. It may be that in this case the peripheral blood was enriched, not with young erythrocytes in general, but with young cells which had achieved a certain degree of maturity and had lost their reticular substance.

In the experiments of series IV the rats were exposed to 97% oxygen for 72 h. According to data in the literature [12], after such an exposure the animals must develop oxygen poisoning and lung lesions. In fact, the experimental rats lost weight for some time (Fig. 3, B) and their respiration rate was considerably increased toward the end of exposure, especially after the animals returned to an

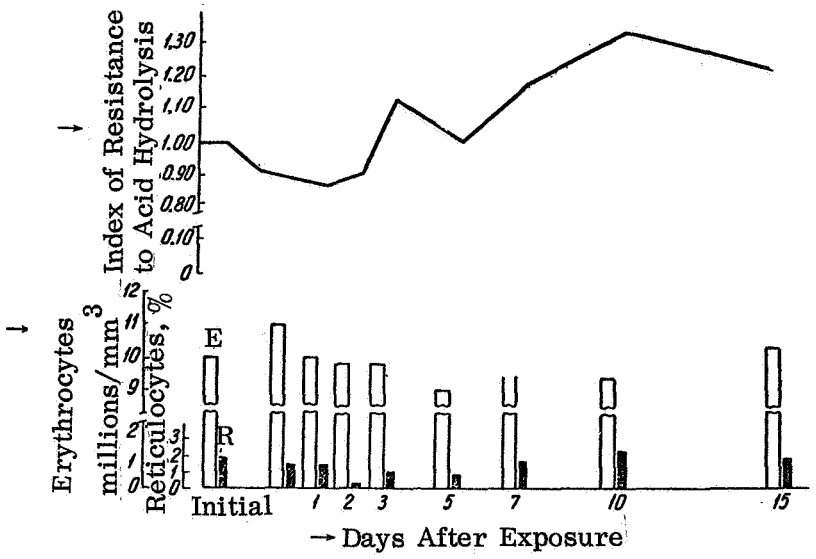

Figure 5. Effect of Exposure for 40 h to O_2 on Red Blood of Rats. Legend as in Fig. 1.

atmosphere of air (Fig. 4, B). In most of the animals autopsied after exposure to oxygen lung lesions were found: hepatization, edema, and pleural effusion. /303

It is clear from Fig. 6 that soon after exposure to an atmosphere of oxygen the number of erythrocytes in the peripheral blood rose and then fell. These changes were more abrupt than in the experiments of series III, although they took place in the same direction.

By the 3rd day after the end of exposure the reticulocyte count had fallen by half, but it then rose again and on the 10th day it had almost regained its initial level. The index of exposure fell considerably soon after exposure, but on the 3rd-6th day it was above its initial value.

As a result of the toxic action of oxygen, stimulation of erythropoiesis evidently took place after a short period of inhibition. The fact that the number of erythrocytes in the blood nevertheless remained low may be interpreted as the result of increased hemolysis.

The results described indicate that a hyperoxic environment has a complex effect on the red blood. This is presumably the reason for the conflicting nature of the results described by different workers studying this problem.

Extensive experiments have shown, for instance, that an increase in the partial pressure of oxygen in the environment may produce an effect on the hemo- /304

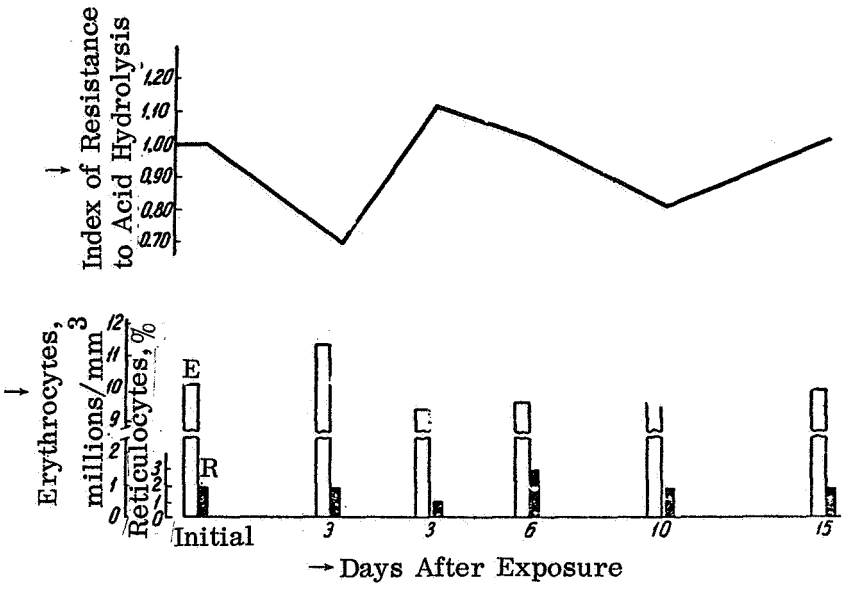

Figure 6. Effect of Exposure for 72 h to O_2 on Red Blood of Rats. Legend as in Fig. 1.

globin concentration, and the erythrocyte and reticulocyte counts in the blood of animals which differs from one case to the next [14].

In our experiments the dynamics of the age composition of the red blood was composed of alternating periods of rise and fall of the percentage of young forms of erythrocytes.

It may be postulated that an excessive oxygen concentration in the blood reduces the natural stimulus to erythropoiesis, i.e., acts in the opposite direction to the effect of oxygen lack. However, this action is complicated by a number of factors. First, sudden exposure to hyperoxia, by causing spasm of the peripheral vessels, retention of blood in storage depots, and other compensatory reactions restricting the supply of oxygen [6], may lead to tissue anoxia, which is especially severe if lung lesions develop. In such cases the hypoxic state of the animal is most acute at the moment of change from an atmosphere with a raised partial pressure of oxygen to a normal atmosphere. The result of this "hyperoxic hypoxia" [4, 9] must naturally be stimulation (and not inhibition) of erythropoiesis.

It is clear from what has been said that the effect of oxygen on the blood system cannot be expected to be consistently in the same direction. Depending on the degree of elevation of the partial pressure of oxygen in the atmosphere and the time spent by the animal in such an atmosphere, as well as on its adaptation to hyperoxic conditions [14], the net result will be either inhibition or stimulation of erythropoiesis.

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